The Human Placental Perfusion Model and Prediction of the In Vivo Transfer of Therapeutic Drugs

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Castellucci & Kaufmann Placenta 1982 3(3):269-85
Factors Influencing Placental Transfer

- Physiochemical properties
  - $pK_a$
  - Molecular weight (<500-600 Da)
  - Lipid solubility

- Pharmacokinetic properties
  - Non-placental
    - Protein binding
    - Maternal and fetal elimination/distribution
  - Placental
    - Transport mechanisms
    - Binding to placenta tissue
    - Metabolism

Models to study drug transfer

- In vivo
  - Animal models
  - Termination of pregnancy
  - Umbilical cord blood

- In vitro
  - Trophoblast cultures
  - Trophoblast tissue preparations

- Computer Models
  - PBPK

  *Placental perfusion is the only experimental method that can be used to study human placental transfer of substances in organized placental tissue*
Validity of the perfusion model?

- Careful validation of this model is needed before it is used routinely to predict placental drug transfer in preclinical evaluation (Ala-Kokko, 2000)

- There is currently no systematic evaluation of the perfusion model in predicting fetal drug exposure
  
  - Discussions are limited to specific drugs or drug classes

Objectives

1. To systematically evaluate the placental perfusion model in predicting placental drug transfer by comparing it to in vivo data.

2. To construct a pharmacokinetic model that best allows prediction of the in vivo maternal-fetal drug distribution at steady state.

3. To provide recommendations to improve the reliability of the predictions provided by the perfusion model.

Methods

- Systematic search for papers evaluating placental transfer of therapeutic drugs using the perfusion model
  
  - Drugs were identified in the papers that met the inclusion criteria
  
  - A subsequent search was performed on each specific drug to locate papers reporting human cord blood and maternal blood concentrations at the time of delivery.
  
  - F:M ratios from perfusion experiments were compared to C:M ratios, both qualitatively and quantitatively.

Hutson et al., Clin Pharmacol Ther (In Press)
Searched "infantile" AND "perfusion" limited to "human" in MEDLINE, EMBASE, EMBASE Classic Search to August 31, 2010. 1732 papers identified. 147 full-text articles assessed for eligibility. 1585 excluded from title, abstract, or language. 89 Perfusion studies included in qualitative analysis. 33 Perfusion studies included in quantitative analysis. 58 excluded - 19 ratio could not be calculated. - 29 no related in vivo data. - 10 inadequate experimental design.

128 drugs evaluated. 70 drugs compared qualitative. 58 drugs with no in vivo data or no perfusion ratio available. 26 drugs compared quantitative. 49 showed placental transfer (F:M 0.1 to 1.0) in both placental perfusion and in vivo. 9 showed limited transfer (F:M < 0.1) in both placental perfusion and in vivo. 12 showed discrepancies. 5 - F:M > 1 observed in vivo, but not in perfusion. 7 - Steady state was not reached in the perfusion or in vivo.

http://www.nature.com/clpt/journal/vaop/ncurrent/suppinfo/clpt201166s1.html
R² = 0.28306

Model to Adjust Perfusion Results

- Limitation of the perfusion model is that it does not incorporate non-placental pharmacokinetic factors
  - ie) maternal and fetal protein binding
    - F:M albumin increases from 0.28 in first trimester to 1.20 at term
    - F:M AAG increases from 0.09 in first trimester to 0.37 at term

\[ F : M = \frac{\% \text{ unbound}_F}{\% \text{ unbound}_M} \times \frac{1 + 10^{(pK_a - pH)_M}}{1 + 10^{(pK_a - pH)_F}} \times \frac{CL_{FM}}{CL_F + CL_M} \]

Valproic acid

- Closed perfusion at SS
  - F:M = 0.90, 0.85 (Barzago, 1996; Fowler, 1989)
  - C:M = 1.51 (total n=37, 5 studies)

- Adjust the perfusion ratio using the F:M equation
  - In vitro protein binding (Froeschler, 1984)
    - Unbound maternal = 15%
    - Unbound fetal = 9.6%
  - Adjusted F:M = 1.67
**Diazepam**

- Closed perfusion at SS
  - F:M = 0.48, 0.55 (Myllynen, 2002)
  - C:M = 1.27 (total n=255, 12 studies)

- Adjust the perfusion ratio using the F:M equation
  - In vitro protein binding (Ridd, 1989)
    - Unbound maternal = 3.24%
    - Unbound fetal = 1.90%
  - Adjusted F:M = 1.2

**Propranolol**

- Closed perfusion at SS
  - F:M = 1.0 (Schneider, 1988)
  - C:M = 0.26 ± 0.62 (n=8, Erkkola, 1992)

- Adjust the perfusion ratio using the F:M equation
  - In vitro protein binding (Belpaire, 1995)
    - Unbound maternal = 21%
    - Unbound fetal = 39%
  - Adjusted F:M = 0.6
Open vs Closed Configuration

- Open configuration underestimates the *in vivo* steady state C:M ratio
- Calculated using initial maternal concentration
- Does not distribute between as the maternal-placental-fetal compartments as it does in vivo
- Useful for calculating clearance calculations
- Caution in comparing results to *in vivo*
  - Example - Alfentanil

Alfentanil

- Weak base, $pK_a=6.5$, bound to $\alpha_1$-acid glycoprotein
- Perfused in open configuration with no protein in the perfusate
  - At steady-state, F:M=0.22 (Zakowski, 1994)
- *In vivo* cord measurements
  - C:M 0.29 – 0.35 in 4 studies (total n=45)
  - C:M ~1.0 for free levels (n=31)

\[
\text{Adjusted F:M} = 0.37
\]
Bupivacaine

- **Closed perfusion experiments**
  - 2% HSA on both sides F:M = 0.81, 0.74 (Johnson, 1995 & 1999)
  - Plasma (M), 4% HSA (F) F:M=0.51, 0.40 (Johnson, 1995 & 1999)

- **In vivo**
  - Free C:M = 0.73 (total n=51, 3 studies)
  - Total C:M = 0.30 (total n=232, 16 studies)

- **Calculated F:M** (using CL, pK\textsubscript{a}, and PB)
  - F:M = 0.28

Limitations

- Can not apply F:M equation when perfusions show limited transfer

Indinavir

- Perfused in open configuration (no protein)
- At steady-state, F:M=0.04, 0.06 (Sudhakaran, 2005 & 2008)

- **In vivo** cord measurements
  - C:M <LOD to 0.08 in 2 studies (total n=25)
  - Adjusted F:M = 0.26

Recommendations

- Publication of perfusion results should report:
  - absolute concentrations
  - placental binding
  - pH of maternal and fetal perfusates

- **In vitro** measurements of protein binding would enhance interpretation of perfusion results

- Whether steady state was obtained
Summary

- A systematic evaluation of the placental perfusion model shows that it is a suitable model to predict placental drug transfer.
- Using perfusion data together with in vitro protein binding experiments in maternal and cord blood would enhance interpretation of results.
- When applied appropriately, the placental perfusion model is an invaluable tool to help guide decisions regarding the benefits and risks of new medications that may be required during pregnancy.

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